52/540

NASA Phase I
Final Report
Contract: NAS9-01028

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imperium
Advanced ultrasonic imaging

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Project Summary

Purpose of the research: With the completion of the International Space Station the level of extravehicular activity (EVA) is set to dramatically expand. Space suits worn by astronauts during EVA are pressurized to 4-5psi, significantly less than the pressure of the space station. These conditions have lead to a concern by NASA regarding decompression sickness (DCS).

In this project we propose to image extravascular gas concentrations hypothesized to be the cause of DCS. It is has been difficult to confirm this hypothesis because to date there is no capability to detect and image extravascular gas bubbles *in vivo*. This is an important need. Existing Doppler ultrasound systems are adequate for the detection of intravascular gas concentrations but insensitive to gas formations in tissue where the motion of gas is limited.

The proposed imaging capability is embodied in Imperium's transmission ultrasound camera. Experiments on rats and human subjects were performed during the course of this Phase I effort.

Description of the research: Using a laboratory system at its Rockville, Md. facility, Imperium has performed a series of experiments to demonstrate the effectiveness of its ultrasound camera in imaging gas bubbles related to DCS. An initial series of laboratory experiments was completed and has demonstrated some encouraging results indicating that imaging DCS bubbles in tissue may be feasible. These experiments were conducted using Imperium's C-scan, through-transmission, real-time ultrasound technology. A test system consisting of a water immersion tank containing interchangeable immersion transducers, a 10" water path for sample placement, and an I-100 Acoustocam imaging system mounted through one of the tank walls was used. All of the images shown in this Phase I final report were taken with a 5 MHz transducer The transducer was 1.5" in diameter and circular with resulting circular image areas.

Project Results: The project was successful in demonstrating that the proposed technique is effective in imaging gas concentrations that are the result of DCS *in vivo* and in real time. The experiments were conducted at the Institute for Environmental Medicine (IFEM) at the University of Pennsylvania. Dr. Steven Thom of IFEM assisted Imperium in performing the experiments. Imperium's ultrasound camera was successful in imaging gas concentrations in rat hind legs and rat brains. A series of experiments were conducted at Imperium as well. These experiments include imaging air in tissue, imaging the contrast agent Levovist® In tissue, and imaging of bubbles caused by a micronucleation process. The results of these experiments were very successful and highly suggestive that the proposed ultrasound technology will be useful in the investigation of DCS. The successful results of this Phase I effort justify a Phase II continuation with the goal of improving the etiology of DCS.

Experiment 1: Air In Sausage

The first experiment was conducted to demonstrate that when air is injected into animal tissue, a visual presentation of the process can be obtained from the ultrasound camera. An air-filled syringe was inserted into a piece of sausage that was placed in the field of view of the ultrasound camera. When the syringe needle entered the sausage an image of the needle was displayed in real time. The camera was operated at 5 MHz, in transmission mode, looking through the sausage. When air was injected into the sausage, a large (black) bubble growing out of the needle tip was displayed. Since ultrasound at the frequency we were using will not penetrate air, the image appeared black.

The photographs in Figures 2a-d display the results of this experiment. Figures 2a and 2b show the insertion of the needle into the sausage prior to the injection of air. Note the relative transparency of the sausage. Figures 2c and 2d show the sausage after the injection of air. Note the presence of a black mass indicating the attenuation caused by the air bubble. An MPEG file of this imaging experiment is included on the CDROM accompanying this report, it is labeled as "Air Into Sausage". As is true with all the images in this report, the motion inherent in the MPEG file accentuates the process being displayed. In this case the process of air being injected into the sausage is much easier to visualize because the motion of the needle and air bubble can be seen.

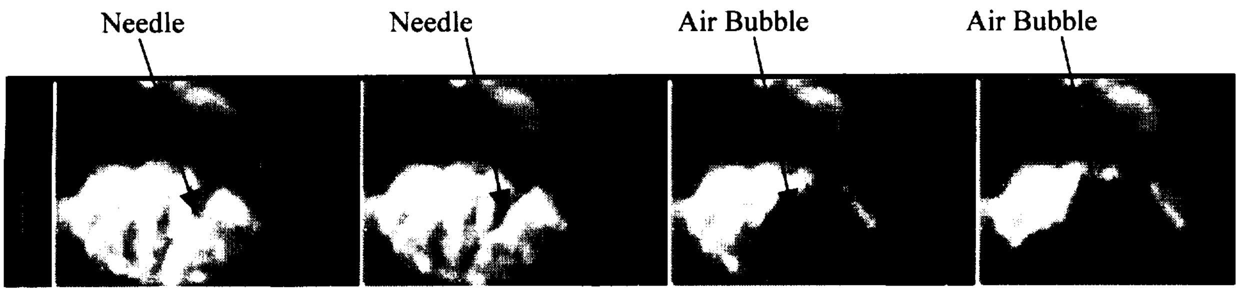


Figure 2a **Figure 2b** **Figure 2c** **Figure 2d**

<u>Point Demonstrated:</u> The point of this first experiment is to demonstrate the sensitivity of the proposed ultrasound technique to the presence of air pockets in tissue. The point was successfully demonstrated. In fact, the proposed ultrasound technique is very sensitive to the presence of air. In most applications the attenuation through air is a hindrance however in this application the contrast between air and tissue is beneficial.

Experiment 2: Bubbles In Soda Water

The next experiment involved imaging a 5MHz ultrasound wavefront passing through a plastic bottle containing club soda. When the soda bottle was unsealed there was the expected rush of bubbles. The ultrasound image displayed many bubbles rapidly rising through the soda. The bubbles again were typically black for the reason stated in experiment 1.

The photographs in Figures 3a-d display the results of this experiment. Figures 3a shows a very transparent image of through-transmission ultrasound through the bottle prior to unsealing the soda bottle. Figure 3b shows the complete attenuation of the ultrasound immediately after the bottle is unsealed and Figure 3c shows the beginnings of ultrasound propagating through the soda a short time after the bottle is unsealed. Figure 3d shows a return to the transmissivity seen before the bottle was unsealed. An interesting effect of the image in Figure 3d is the dark ring around each bubble with apparent lesser attenuation in the center. This phenomenon is caused by a refraction edge effect around an impedance boundary in the transmission path. The severe impedance mismatch between the soda water and gas bubbles in the water causes the ultrasound wavefront to bend around the circumference of the bubble. This effect is the subject of study at Imperium and may be useful in the measurement of concentrations of nitrogen bubbles that occur during decompression. Consider that the extent of refraction is a function of the impedance mismatch. It is proposed that the extent of this refraction may be proportional to the impedance mismatch and so may be a measure of the volume of nitrogen present. An MPEG file of this imaging experiment is included on the CDROM accompanying this report, it is labeled "Soda Bottle". The motion of the bubble formation is quite dramatic in the MPEG video clip and serves to accentuate the visualization of process observation.

Figure 3a **Figure 3b** **Figure 3c** **Figure 3d**

Point Demonstrated: The points of this experiment are twofold. The first is to demonstrate that individual bubbles can be imaged if the bubbles are of sufficient size. The size of the bubbles generated by the club soda was not measured but could be seen to be at least several millimeters in size. The second point is that clouds of bubbles generate high levels of attenuation (Fig. 3b). This second point is important because in the investigation of DCS, we will most likely be imaging volumes of gas not individual bubbles.

Experiment 3: Process of Micronucleation

The mechanism by which nitrogen bubbles are formed during decompression is currently a matter of speculation. It is known that a static volume of blood subjected to pressure and then decompression does not form these bubbles. There are several theories regarding this subject one of which is the theory of micronucleation. Nitrogen excreted from tissue in gas phase during decompression bonds to a substance that serves as the nucleus of a gas bubble. Experiment 3 is concerned with demonstrating the principle of micronucleation. Club soda with its large volume of dissolved CO_2 is used as the medium in which the bubbles are to form and salt is used as the substance which serves as the bubble nucleus.

The photographs in Figures 4a-d display the results of this experiment. The video in Figure 4a shows a cup of soda water immersed in a tank of water. Note the camera on the left side of the picture and the ultrasound transducer on the right side. This is a typical system configuration used by Imperium for through-transmission experiments. The image inset in the upper left corner is the ultrasound image taken simultaneously with the video. Note the transmissivity of the club soda with bubble formation. Figure 4b shows a snapshot of the experiment taken immediately after salt is added to the club soda. The ultrasound image is completely black indicating a high level of attenuation through the medium. Note the foam present in the cup indicating a large volume of bubble formation. This bubble formation is a result of the CO_2 precipitating out of the soda water and bonding to the salt crystals. Figures 4c and 4d show a gradual decrease in the level of attenuation as the bubbles rise to the top of the cup and are expelled from the soda water. An MPEG file of this imaging experiment is included on the CDROM accompanying this report, it is labeled "Salt in Soda Water".

Figure 4a

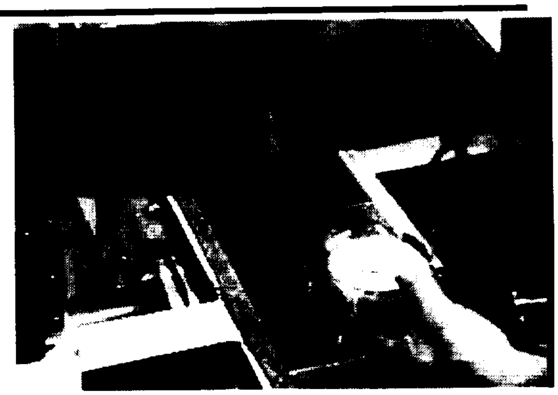


Figure 4b

Figure 4c

Figure 4d

Point Demonstrated: The point of this experiment is to demonstrate that the process of micronucleation can be observed by the proposed ultrasound technique. As will be discussed in Part 5 of this proposal, monitoring the process of bubble growth during decompression will be as important part of the Phase II effort. While the time frame and quantity of bubble formation during decompression is expected to be different from the experiment performed here, simply observing the process which may be the cause of DCS was agreed by Imperium's staff to be a useful exercise.

The detection of bubbles of the size encountered in DCS is more problematic than detection of the bubbles shown in experiments 2 and 3. The limit of the resolution of the ultrasound camera is about 450 microns as determined by the frequency employed and the f-number of the camera lens. A higher frequency would improve the resolution but not enough to detect individual DCS bubbles. However, we expect to visualize these bubbles as aggregate clouds of Rayleigh scatterers. Scattering of ultrasound occurs when an incident wave is reflected in many directions after interacting with a structure whose dimensions are similar or less than the wavelength of the ultrasound. A case of particular importance for our need is one in which the dimensions of the structures are much smaller than the wavelength. Here scattering occurs equally in all directions: it is known as Rayleigh scattering. In ideal Rayleigh scattering the amount of scattered ultrasound varies with frequency to the fourth power. These considerations have led to the use of ultrasound contrast agents based on microbubble suspensions for a variety of medical applications. Besides vascular applications, it has been reported that injection through needles of a small amount of microbubble-containing contrast agent has been used to improve needle localization during ultrasound guided biopsy or drainage procedures.

Imperium has purchased a quantity of Levovist® which is an ultrasound contrast agent. Levovist® is a palmitic acid stabilized microbubble agent in which the microbubbles are filled with air. With proper preparation, the Levovist® solution is stable for 10 minutes. 90% of the bubbles in Levovist® are less than 10 microns in diameter which allow the bubbles to pass through lung capillaries. This feature allows the contrast agent to travel through the entire vascular system. The concentration of microbubbles in a contrast agent solution is determined by the proportion of microparticles suspended in solution. Levovist® has microparticle concentrations of 200mg to 400mg per 1ml of solution. The total amount of air per 1g of microparticles is less than 100μl.

Levovist is an example of a scatterer of ultrasound that assumes the Rayleigh condition is met. That is, the scatterer is minute compared to the wavelength λ. Expressed differently, $kr << 1$ where k is the wavenumber equal to $2\pi/\lambda$ and r is the radius of the scatterer. The scattering cross section is given in equation 1 as:

$$\sigma = 4\pi/9\ k^4 r^6 (F(M)) \qquad \ldots(1)$$

where F(M)) describes the compressiblity and density of the gas. F(M)) distinguishes the features of different contrast agents. We will not need to discuss this further since we are only interested in the case of nitrogen in tissue so we can consider F(M)) a constant. Notice that the scattering cross section increases with frequency to the fourth power and size to the sixth power. Gas which is opaque to ultrasound in the 5MHz region of interest makes the best scatterer.

Experiment 4: Turbidity as a Result of Injecting Fluid into a Static Medium

Before experimenting with the Levovist® it was agreed by Imperiums staff that the effects of turbidity must be evaluated. The process of injecting a fluid into a static medium is bound to create some turbulence and so have some effect on the visual presentation of that medium. If that effect is such that the attenuation of medium is similar to that expected from the contrast agent then the experiment is compromised. This experiment was conducted by injecting water though a syringe into water. Clearly, the density of the water in the tank and the water injected from the syringe are the same. Any visual effects noted will be a result solely of the turbidity of the injection process.

The photographs in Figures 5a and 5b display the results of this experiment. Figure 5a shows the needle prior to the injection of water into the tank. Figure 5b displays a small amount of turbulence which occurs as the water is injected from the syringe. Unfortunately Figure 5b does not provide a good presentation of the turbulence seen in this experiment. The MPEG video clip accompanying this report gives a much better picture. To understand why Figure 5b is so poor it is necessary to make a small digression into the details of the MPEG process. MPEG files are a series of index frames linked together by a sequence of motion vectors. There may only be one index frame once every several seconds. The MPEG codec which was used to capture the video sequences included in this report can only capture still images from the index frames. Imagery captured between the index frames can be displayed in the MPEG video but cannot be captured as still pictures. It was the bad luck of this experiment that none of the MPEG index frames captured the full extent of the turbulence. The MPEG video clip which accompanies this report does display the turbulence with good detail. Examination of the MPEG video clip shows that the turbulence in no way is similar to the attenuation of the Levovist® injections described in experiment 5. The MPEG file of this imaging experiment included on the CDROM is labeled "Water into Water".

Turbulence

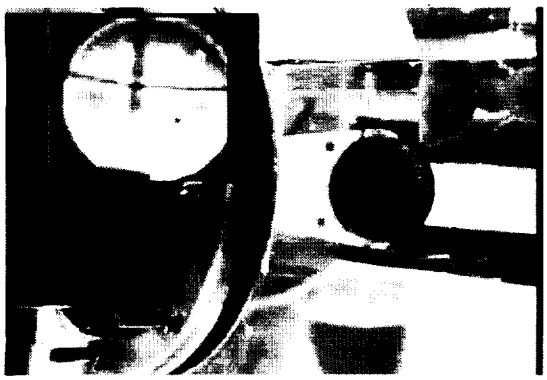


Figure 5a Needle in Water

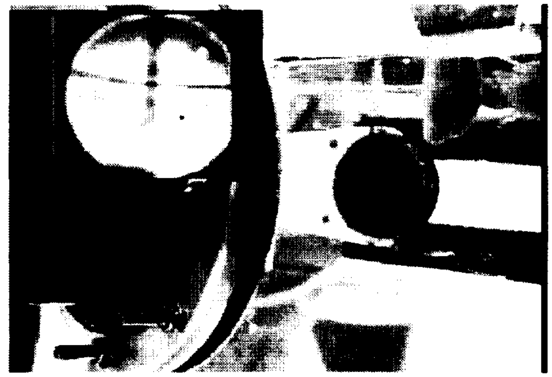


Figure 5b Turbulence in Water

Point Demonstrated: The turbidity caused by injecting water has only a small visible impact on the presentation of the subject material (water). We can therefore assert that when the contrast agent Levovist® is injected, changes to the video presentation of the subject material are caused by the contrast agent itself and not the injection process.

Experiment 5: Attenuation Though Levovist®

As discussed, Imperium has purchased a quantity of Levovist® with the intent of simulating the attenuation we expect from nitrogen bubbles resulting from decompression. Two experiments were performed, injection of Levovist® into water and injection into liver. The first of these experiments was performed to provide a clear image of the attenuation of the contrast agent in a very low attenuation transmission medium. The second experiment was performed to provide an indication of what the attenuation of the contrast agent will look like in tissue and by inference, what the attenuation of nitrogen bubbles caused by decompression will look like.

The photographs in Figures 6a-d display the results of this experiment. A single picture is used to show the results of injecting Levovist® into water. In Figure 6a observe the black cloud emanating from the tip of the needle. This black cloud is the Levovist®. The attenuation through the cloud of Levovist® is such that there is no pixel amplitude. If the attenuation is indicative of the nitrogen bubbles resulting from decompression, the contrast between the tissue and bubbles should be sufficient to resolve the two.

Figure 6b shows a picture of the Liver with needle placed prior to the injection of the Levovist®. Observe the structure of the liver tissue. It is expected that the tissue to be imaged in Phase II as a part of the effort to monitor DCS bubble growth will exhibit similar structural complexities. Resolving DCS bubbles in the presence of these tissue structures will be an important test of the effectiveness of the proposed ultrasound technique. Figures 6c and 6d show the injection of Levovist® into the liver. Observe that the contrast between the Levovist® and the liver is pronounced.

The experiments of injecting Levovist® into water and liver are documented in MPEG files (5) "Levovist® into Water" and "Levovist® into Liver". As with the other experiments described in this report, the motion imparted in the MPEG video clip accentuates the presentation of the process being observed, making the visualization of the injection of Levovist® more pronounced.

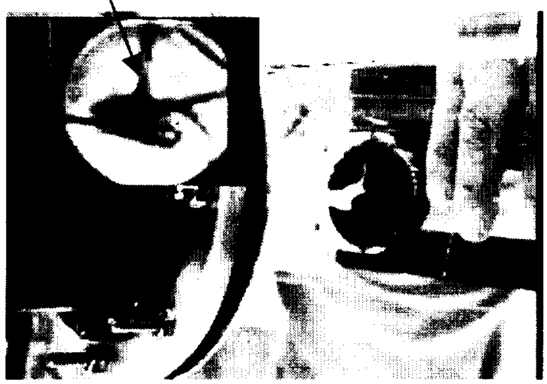


Figure 6a Levovist in Water

Figure 6b Liver Tissue

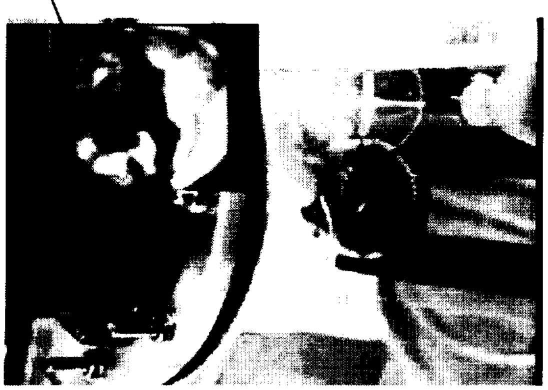


Figure 6c Levovist in Liver

Figure 6d Levovist in Liver

<u>Point Demonstrated:</u> The contrast agent in through-transmission mode shows up clearly. Doppler is not required. It was demonstrated that the contrast agent can be imaged in tissue and doesn't require Doppler or motion. It therefore offers the real opportunity to image DCS related bubbles in biological material.

Experiment 6: Imaging Through A Human Hand

The following experiment is included to demonstrate the spatial resolution of the proposed ultrasound technique and its ability to focus at depth. Figures 7a and 7b show a human hand imaged by Imperium's ultrasound camera. Observe the through-transmission imaging modality. The hand is shown in the middle of each picture. On the left side each picture is shown the acoustic lens which is attached to the camera. On the other side and pressed against the hand is shown the ultrasound transducer. The transducer is electrically excited and an ultrasound wavefront is generated which propagates through the medium, in this case water and the hand. The ultrasound wavefront passes through the acoustic lens which focuses acoustic energy from the object plane onto the image plane of the ultrasound detector array. For more information on the operation and theory of Imperium's ultrasound camera, see our web page at www.imperiuminc.com.

Figure 7a shows a picture of the finger. Note the presence of the bone, tendons and other structures. The image is clearer because of the lack of speckle that is common in other ultrasound imaging modalities and the lack of geometric distortion. Figure 7b shows a picture of the web between the thumb and forefinger. Observe the structure imaged by the ultrasound camera. The picture clearly shows the presence of blood vessels, muscle, and other structures. An MPEG video clip of this experiment is included on the CDROM accompanying this report. The file is labeled "Johns Hand". The motion imparted in the video clip gives a clearer presentation of the structures in the hand than is shown in the still pictures in Figures 7a and 7b.

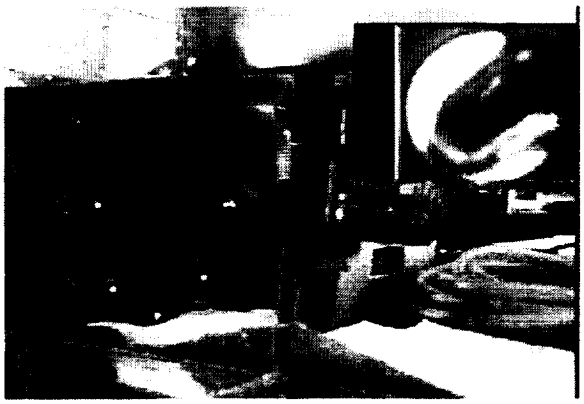


Figure 7a Picture of Finger

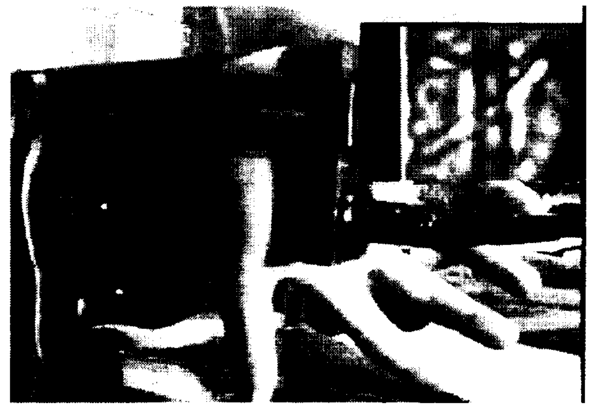


Figure 7b Picture of Hand

Point Demonstrated: The images shown in Figures 7a and 7b demonstrate the resolution of the proposed ultrasound technique and the ability to focus at depth. As will be discussed in Part 5, Imperium is proposing to localize the nitrogen bubble mass to a specific tissue within the lab animals subjected to compression and decompression. The ability to focus at depth allows localizing of the bubble mass in the axial dimension (Z axis).

Experiment 7: Imaging Through A Human Leg
It is expected that imaging of the human body, particularly the extremities where DCS often strikes, will be desirable. To demonstrate the capability of the proposed ultrasound technique to penetrate the human body, the leg of one of our Imperium employees was imaged. The MPEG file of this imaging experiment is included on the CDROM accompanying this report, it is labeled "Steves Leg". Figure 8a shows an image of the calf and Figure 8b shows an image of the arch of the foot. The structures shown in these pictures are more clearly seen in the MPEG video clip.

Figure 8a

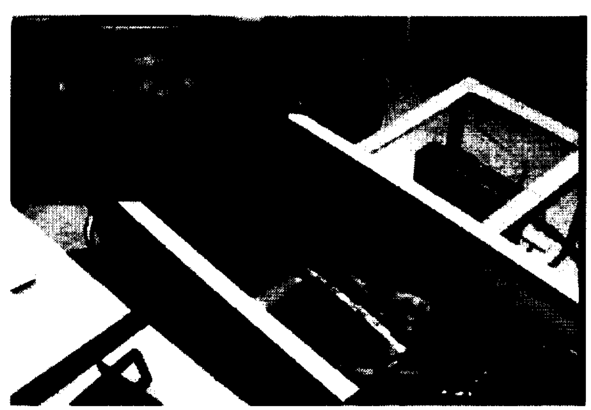


Figure 8b

Point Demonstrated: Penetration of the lower leg is feasible with the proposed ultrasound technique. Given this capability it should feasible to detect the presence of DCS bubbles in tissue of the human leg.

Experiment 8: Detecting the Presence of Gas Related to Decompression in Rats

The culmination of the Phase I effort was a trip to the Institute for Environmental Medicine (IFEM) at the University of Pennsylvania. Dr. Steven Thom of IFEM assisted Imperium in performing the experiments. A summary of the facilities at IFEM is given in Part 7, Facilities and Equipment. A population of eleven rats was subjected to a time-pressure profile of 6atm for two hours. Decompression was accomplished at a rate of 88ft./min. The hyperbaric chamber used in this series of experiments in shown in Figure 9. The ultrasound camera used in these experiments included a 1" FOV lens and 5MHz transducer from Panametrics. A picture of the tank and camera is shown in Figure 10. All of the rats were alive during the compression and decompression sequence. All of the rats died as a result of the decompression procedure or were sacrificed afterward.

Figure 9 Small Hyperbaric Chamber

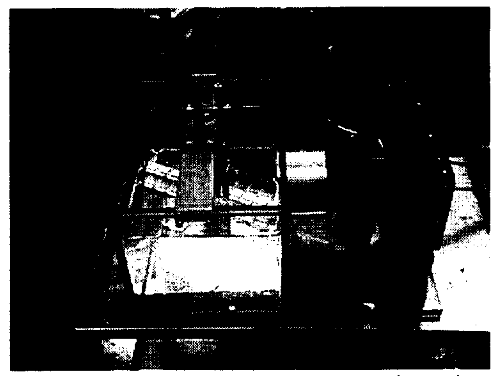


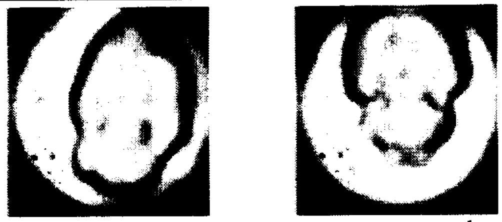
Figure 10 Imperium Camera and Tank

The results from experiments on rat #6, rat #7, and rat #11 are included in this report. Two areas of the rats were imaged, the hind leg and the brain. The hind leg represents a muscle that moves and it is expected that gas concentrations will be formed in this area due to stress assisted nucleation. The brain represents a solid organ in which no motion occurs. As will be seen, gas concentrations did occur in the brain which suggests the possibility that there are other mechanisms responsible for the formation of gas concentrations due to decompression. Rat #6 and rat #11 were chosen for inclusion in this report because both the brain and the hind leg areas of these two rats were imaged and because the response of these two individual rats to decompression were so different. Figure 11 shows the brain of rat #11 after decompression and after the rat had been sacrificed. Note the attenuation through the brain indicating the presence of large amounts of gas. The brain of rat #11 was then recompressed and the attenuation was significantly reduced indicating that the gas had been reabsorbed back into the brain tissue.

Decompressed Decompressed Recompressed Recompressed

Figure 11 Brain of rat #11

The brain of rat #6 shows a completely different reaction to decompression. Figure 12 shows a low level of attenuation of through the brain of rat #6 after decompression indicating that no gas formed. Rat #6 was pretreated with Hyperbaric Oxygen (HBO) at 2.8 atmospheres for 45 minutes prior to compression. It is likely that the HBO pretreatment is responsible for absence of gas formation.



Decompressed Decompressed

Figure 12 Brain of rat #6

The hind legs of rat #11 and rat #6 also show dramatic differences in the response to decompression. Figures 13, 14, and 15 show rat #11 before decompression, two minutes after decompression, and seven minutes after decompression.. Rat #11 was alive during the images taken in Figures 13 and 14 but had died prior to the pictures taken in Figure 15. Figure 13 is a control set of images showing the rat prior to compression. Note the relative level of attenuation and the clear presence of bone structure and the Femoral artery. Figure 14 shows rat #11 two minutes after decompression. Note the much higher level of attenuation through the leg. The images in Figure 15 are almost completely opaque indicating a large quantity of gas formation.

Figure 13 Rat # 11 Hind Leg Before Decompression

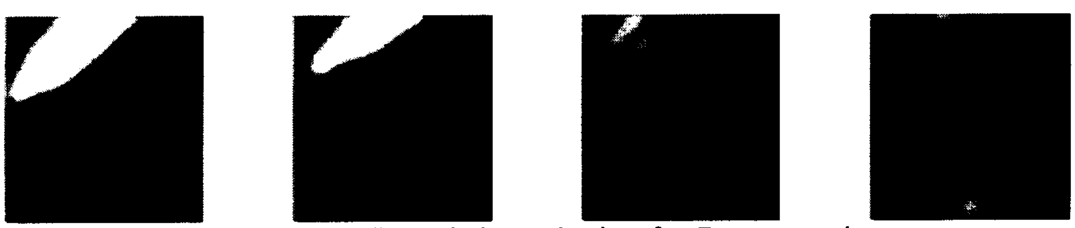


Figure 14 Rat # 11 Hind Leg, 2 min, after Decompression

Figure 15 Rat # 11 Hind Leg, 7 min, after Decompression

Rat #6 was subjected to the same time-pressure profile with very different results. Again, it must be noted that rat #6 was pretreated with HBO. Figure 16 shows rat #6 prior to compression, note the relatively low level of attenuation. Figure 17 shows rat #6 immediately after decompression. Note the clear image of a gas bubble in the Femoral artery. Figure 18 shows rat #6 210 minutes after decompression, note the general darkening of the tissue and the presence of bubbles in the tissue.

Figure 16 Rat # 6 Hind Leg Before Decompression

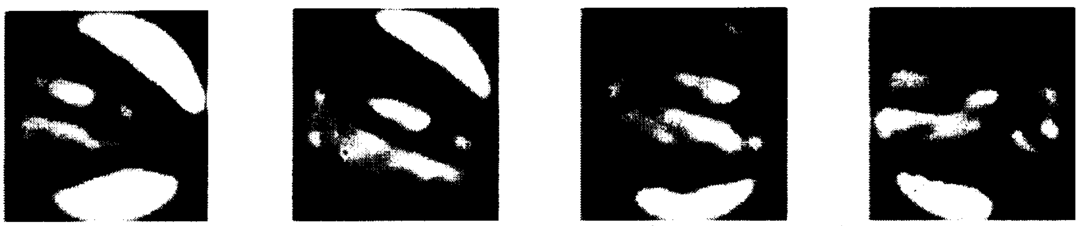


Figure 17 Rat # 6 Hind Leg, 0 min, after Decompression

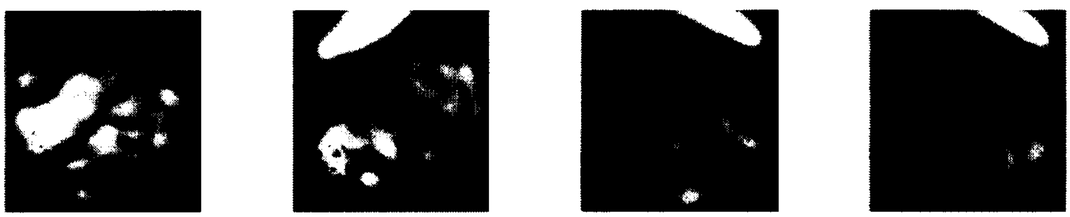


Figure 18 Rat # 6 Hind Leg, 210 min, after Decompression

Rat #7 is included in this report to demonstrate the effects of recompression. Figures 19 and 20 show rat #7 before and after decompression. Note the high level of attenuation n Figure 20. Figure 21 shows rat #7 after recompression, note the decrease in the level of attenuation as the gas is reabsorbed back into the tissue.

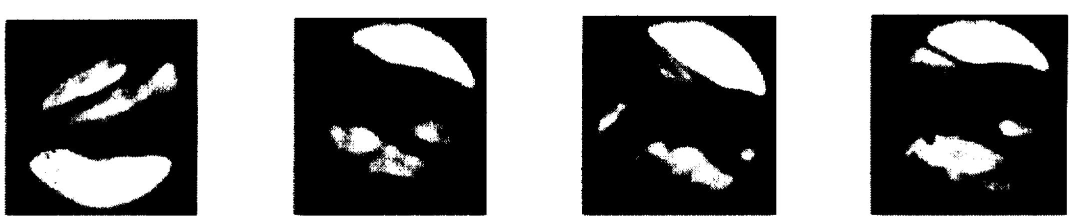


Figure 19 Rat # 7 Hind Leg Before Compression

Figure 20 Rat # 7 Hind Leg, 5 min. After Decompression

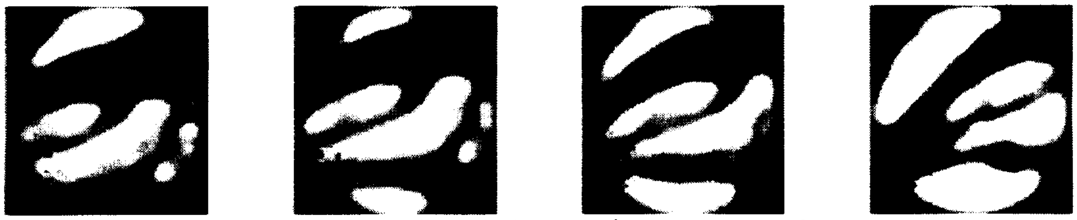


Figure 21 Rat # 7 Hind Leg, After Recompression

MPEG video files for each of the still image sequences in this report are included in a CDROM accompanying this report. Only the videos associated with the still pictures in this report are included on the CDROM. There are MPEG video files and still pictures for each of the eleven rat subjects which were a part of this experiment. If there is an interest in viewing a video or still picture not included on the CDROM, please contact Imperium at 240-453-6236. Table 1 provides an index for the MPEG files on the CDROM.

Item	File Name	Description
1.	PR16-R6-control	Rat #6 Hind Leg, Before compression / decompression
2.	PR2-24-DC6-0	Rat #6 Hind Leg, 0 min. after decompression
3.	PR2-52-DC6-210	Rat #6 Hind Leg, 210 min. after decompression
4.	PR2-54-DC6-brain	Rat #6 brain after decompression
5.	PR18-R7-control	Rat #7 Hind Leg, Before compression / decompression
6.	PR2-25-DC7-5	Rat #7 Hind Leg, 5 min. after decompression
7.	PR2-34-RC7-0-dead	Rat #7 Hind Leg, 0 min. after recompression
8.	PR2-32-DC11-control	Rat #11 Hind Leg, Before compression / decompression
9.	PR2-41-DC11-2	Rat #11 Hind Leg, 2 min. after decompression
10.	PR2-44-DC11-7	Rat #11 Hind Leg, 7 min. after decompression
11.	PR2-49-DC11-brain	Rat #11 brain after decompression
12.	PR2-55-RC11-brain	Rat #11 brain after recompression

Table 1: Index of MPEG Files

Commercialization and Phase-III Plans

Product or Service Commercial Feasibility
Imperium is focused on the development of next-generation ultrasound imaging systems. We have identified four areas of commercial application for these systems, shown in Figure 39 below. These are non-destructive testing, industrial imaging, medical imaging, and undersea imaging. Imperium is pursuing the deployment of commercial systems in these areas and the research proposed for a DCS is directly applicable to these applications.

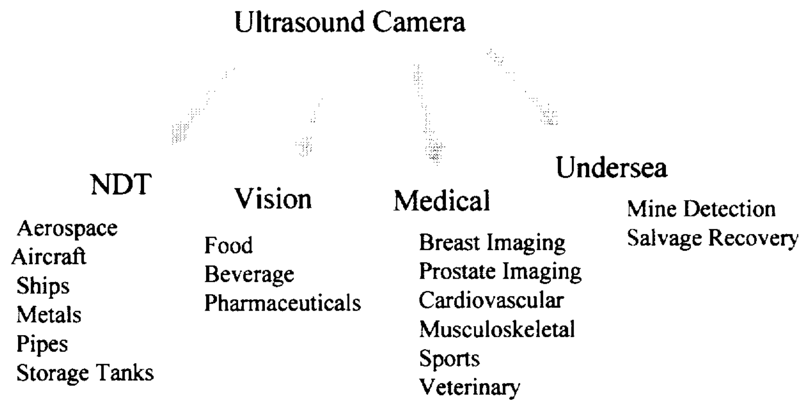


Figure 39

The ultrasound technology that is the focus of this proposal generates images that inherently exhibit higher resolution than current ultrasound systems. Images resemble real time x-rays and thus are easier to interpret. The images are generated without any radiation. In addition, due to its semiconductor based design, the system is easier and cheaper to build. This enabling technology is a completely noninvasive ultrasound 'camcorder'. Although there are numerous commercial and government applications of the device, the product development focus can be grouped into two sectors: Industrial use and medical use.

The larger market application is for medical imaging and this will be the initial focus of Imperium's commercial efforts. There is an opportunity to change the way medical imaging is practiced through Imperium's high-resolution ultrasound technique. Clinicians are continually looking for tools that directly visualize internal structures (just as they learned in medical school).

Ultrasound is ideal for looking at soft tissue structures. These include internal organs, fetuses, vessels, arteries, lesions, tumors, etc. Ultrasound is a popular modality and the fastest growing imaging technique. The popularity of ultrasound is partially because it is non-invasive, does not use ionizing radiation, and is portable. Current ultrasound requires trained technologists to perform the exams and specially trained physicians to interpret these exams.

Compared to other modalities such as X-ray and MRI, current ultrasound also has poorer resolution and unwanted artifacts. Furthermore, a high performance ultrasound machine costs over $200,000. In production, the Imperium device will be under $50,000, low enough for a private clinician to justify its purchase, in addition to traditional hospitals and imaging centers.

Our camera could represent a breakthrough in medical imaging. The technology exhibits images that are "x-ray like", with no unwanted artifacts and high resolution. This means that ultrasound can now be used where it could not before. Furthermore, current ultrasound markets could be expanded. The technology can be produced much cheaper than today's ultrasound machines and can be used by non-specialized clinicians and technologies. Therefore, with the added capabilities and lower cost, it opens up the opportunities of ultrasound into several untapped, very large markets.

Dr. Matthew Freedman, Clinical Director of the Department of Radiology at Georgetown University Medical Center, as well as a member of Imperium's Clinical Advisory Board, describes our technology :

> *"The images shown provide additional information beyond that seen by conventional ultrasound, combining the images visible on conventional ultrasound and x-ray mammography. The device would appear to have likely applications for evaluating tendons of the extremities following trauma. It would be far cheaper to use than MRI and could be used interactively for guiding procedures in the breast, prostate, and pediatric brain in real time".*

For clinical use, new imaging technology must provide better imagery and must either shorten the length of the exam or the dependence of the operator. The ultrasound camera can do all of this. High quality imagery means less setup time and less dependence on specialized interpreters. Embodiments of the technique have been designed on a cart for -portable needs or an even more compact, handheld, LCD-based system for walking from room to room.

The near term clinical applications of the technique are musculoskeletal imaging and biopsy guidance. These initial applications were selected by our Clinical Advisory Board and validated through a series of surveys performed by a medical imaging consulting firm. These opportunities were then married with Imperium's technology set and a clinical roadmap was developed.

A concept drawing of the clinical imager is shown below. Some ultrasound gel is placed on the target to be inspected. The patient simply places the extremity or body part between the two pliable bags and the technician or clinician observes subsurface structures *as they move*. The device can reach a variety of musculoskeletal parts from the shoulder to the foot. The patient does not feel anything other than the probe touching the skin.

The space between the sending and receiving portions of the camera module is adjustable to accommodate different body parts. Also, the entire arm moves up and down with various degrees of freedom. Images are shown in real time on the monitor and can be stored, annotated, reviewed, or remotely transferred over the Internet using standard medical imaging protocols.

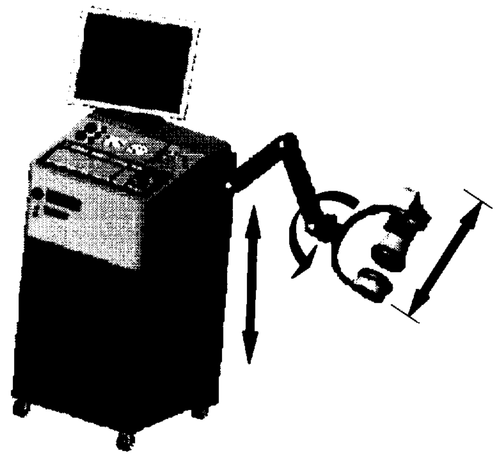


Figure 40

For industrial use, also known as nondestructive testing (NDT), our technology provides a unique capability to generate subsurface images of a variety of industrial components.
For industrial markets, Imperium offers the capability to "see" inside industrial products. Cracks, corrosion, voids, and other flaws are often detected by ultrasound today. However, this nondestructive testing (NDT) is very time consuming to perform and requires highly trained operators. Using the ultrasound camera, the operator simply places a hand held probe against the target and view subsurface images on a LCD. Applications include the real time inspection of the following:

- Storage tanks
- Pipes
- Aircraft
- Ships
- Bridges
- Packaged semiconductors
- Composite materials
- Metal materials
- Foreign objects in meats and fish
- Foreign objects in packaged goods
- Foreign objects in pharmaceuticals

Figure 41 shows a handheld prototype of this type of application.

Figure 41

For NDT use, the Imperium device offers the following competitive advantages over current NDT inspection techniques:

- Designed specifically for the evaluation of hidden structures and materials,
- Proven in its capability to detect materials defects, corrosion, and cracked rivets,
- Applicable to the monitoring of complex composite materials manufacturing processes,
- Unaffected by target surface geometry,
- Low cost,
- Small, light weight, and low power, and.
- Designed for real-time in-situ NDE.

Once the performance of the new ultrasound array and camera are validated through the work to be performed during this program, the technical risk becomes small. The effort will revolve around engineering mechanical embodiments of the camera to meet the needs of the industry.

Market Feasibility and Competition

It is anticipated that musculoskeletal imaging be selected as the first clinical application for our device. There is a major need today to clinically investigate soft tissue structures. Radiologists and orthopedists have great difficulty in dynamically visualizing the soft tissue features of ankles, knees, wrists, and hands with current ultrasound. Tendon tears, injuries, osteoarthritis, Achilles tendon conditions, infected joints, and embedded foreign objects could be visualized dynamically without radiation. One radiologist surveyed said he could increase his number of procedures by 10-15% if he could do high resolution musculoskeletal imaging ultrasonically. Potential users include radiologists, sports medicine specialists, emergency room physicians, and orthopedic surgeons. To serve this multi-faceted user group, it is anticipated that multiple systems will be required in each hospital. As a minimum, the radiology department, orthopedic surgery, the hand clinic, and the emergency room could have one unit each totaling four units per hospital. For musculoskeletal imaging, the primary hospital market in the US of 2,150 institutions provides a market potential for the camera is 8,600 units or $430 million. The total potential world market is $1.1 billion. The total market for all medical imaging applications is $4.3 billion. For both medical and NDT markets, the total market is estimated at $5.4 billion. The government represents approximately 15% of this total estimate.

One very attractive element of this opportunity is the lack of competitive threat to this technology. This is seeded in intellectual property position, trade secrets, technical know-how, and many years of experience with the technology. This provides Imperium with the necessary market jump in the field. As discussed above, we have a patent issued on the ultrasound array and have several other patent applications either pending or being written.

Imperium's strategy is to back up its strong technology capabilities with a strong intellectual property position. This strategy includes patents, both granted and pending, as well as trade secrets and technical know-how not disclosed in patents but are required to make the technology function. We are consistently strengthening our intellectual property position with additional broad patents that will maintain our position for many years into the future.

When collaborating with key academic and research institutions regarding specific applications of the technology and clinical measurements, we have entered, and will continue to enter, into joint development agreements which provide Imperium rights to any resulting intellectual property, including rights to any patent applications filed in accordance with the collaboration.

Imperium's intellectual property strategy will also include the pursuit of international rights in a manner consistent with its long term marketing and manufacturing plans. This will include the filing of patent applications in those countries and/or pursuant to international treaties, deemed strategically important to Imperium's business.

Strategic Relevance to the Offeror

Imperium is focused solely on the development and marketing of the ultrasound device which is the focus of this proposal. The company was formed specifically for this purpose and does not solicit any business which is not in direct support of the technology. One of the attractions of Imperium is that there is no other provider of this system. With the advancement of the technology and our intellectual property position, the plan is to pursue the variety of commercial markets aggressively over the next several years.

Key Management, Technical Personnel and Organizational Structure

Since the ultrasound camera represents the unification of several industry and engineering disciplines, we have brought together a highly diverse team of individuals uniquely qualified for this venture. Organized into three functional operations shown below, the company is heavily reliant upon the Clinical Advisory Board (CAB) as well as external technical and marketing expertise. The Clinical Advisory Board (CAB) is a group of prestigious radiologists, orthopedic surgeons, and experts in the ultrasound field, were selected for their pioneering work in proven and lasting medical imaging advancements. They have been and will continue to be the primary counsel for clinical issues up to and following commercial release.

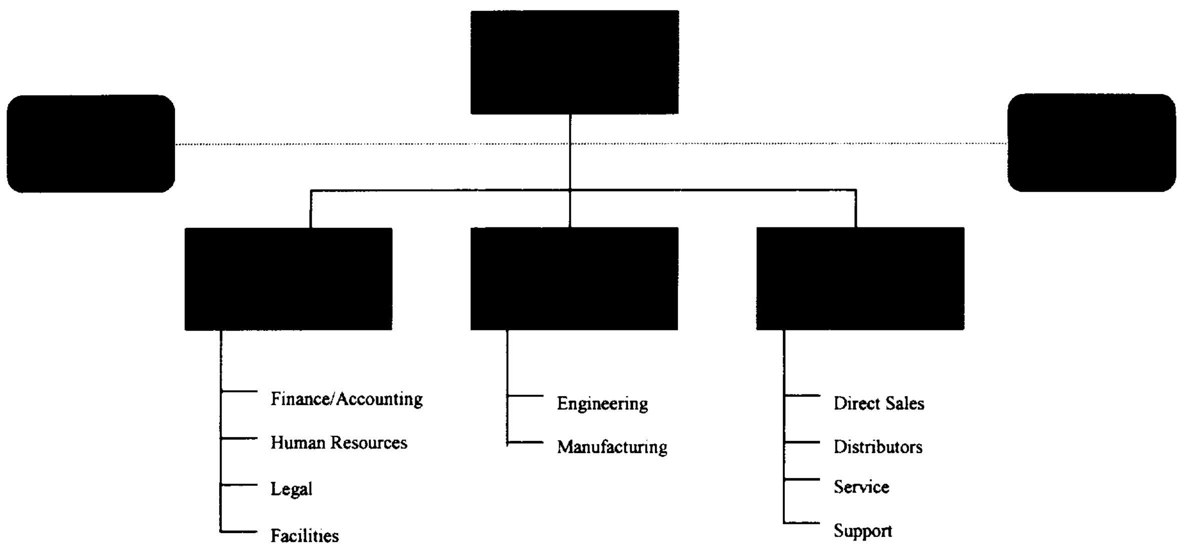


Figure 42

Summary descriptions of management experience are provided below:

Dr. Marvin E. Lasser, President – Dr. Lasser has been developing novel imaging technologies and product development for over 40 years. His past experience includes appointments as the Chief Scientist of the US Army and Director of Army Research. During his seventeen years as Chief Scientist of the US Army, he managed all basic and applied research that the Army performed, with an annual budget of $800 million. Prior to his appointment as Chief Scientist, he was the Director of Research at the Philco/Ford Corporation.

Mr. Robert Lasser, Vice President – Mr. Lasser has been involved in sales and marketing activities for 11 years. He has been responsible for the quantifying and developing, and educating several new markets for Imperium's technology, including generating Imperium's revenue to date. This revenue was generated from very early prototypes with very limited performance. He is the former Manager of Pre-sales at Manugistics, Inc. of Rockville, Maryland. During this time, Manugistics went from $10M to $50M in sales, including a successful Initial Public Offering (IPO). He is responsible for Imperium's strategic market direction and business planning.

Mr. David Rich – Director, Engineering – Mr. Rich has more than 20 years of experience in product development and manufacturing, with an expertise in electrical engineering and software. He is an expert in the design, test, and quantity production of electronic systems. This includes acoustic systems and sensors as well as video systems. Mr. Rich has led the design effort which successfully produced some of our early camera systems. Mr. Rich will continue to be responsible for all product development efforts as well as ramping up for volume production.

Our personnel requirements are as follows:

	Aug 2001	Aug 2002	Aug 2003	Aug 2004	Aug 2005
Headcount	7	18	30	48	72

Current Imperium staff also includes laboratory, software, and mechanical expertise. During the next 18 months, key hires include a VP of Marketing and a product development manager, both with a background in ultrasound imaging, as well as a company Controller.

Production and Operations: Describe: (a) business development progress to date regarding the contemplated commercial venture; (b) obstacles, plans, and associated milestones regarding all key business development elements; and (c) sources and components of private physical resources committed to date and plans for obtaining the balance of the necessary physical resources.

Financial Planning:

Company financial statements are shown below (unaudited):

Profit & Loss Statement: 2000 - 2004 (in thousands)

	2000	2001	2002	2003	2004
Sales					
Product Revenue	298	550	3,550	17,850	41,700
Government Contracts	376	302	690	2,650	7,200
Other Revenue	2	65	354	1,250	3,300
Total Sales	676	917	4,594	21,750	52,200
Less: Distributor Discounts	0	0	0	3,570	8,340
Net Revenue	**676**	**917**	**4,594**	**18,180**	**43,860**
Cost of Goods Sold	126	150	866	1,588	3,336
Gross Profit	550	767	3,728	16,592	40,524
Operating Expenses					
Sales & Marketing	70	546	2,785	2,400	4,023
Service	87	420	965	1,580	3,021
Product & Mfg Development	430	1,141	2,280	5,350	8,850
G & A (without Depreciation)	87	417	724	1,382	2,035
Subtotal Operating Expenses	674	2,524	6,754	10,712	17,929
Depreciation Expense	6	31	56	159	237
EBIT	(130)	(1,788)	(3,082)	5,721	22,358
Interest Income	2	75	140	240	465
Previous (Loss) Carry Over	(25)	(153)	(1,866)	(4,808)	0
Taxable Income	(153)	0	0	1,153	22,823
State Tax	0	0	0	81	1,598
Federal Tax	0	0	0	392	7,760
Subtotal Taxes	0	0	0	473	9,357
Net Income After Taxes	(153)	(1,713)	(2,942)	5,488	13,466

Table 3

Cash Flow Statement: 2000 - 2004 (in thousands)	2000	2001	2002	2003	2004
Sources					
Net Income (Loss) After Taxes	(153)	(1,713)	(2,942)	5,488	13,466
Add: Depreciation	6	31	56	159	237
Subtotal from operations	(147)	(1,682)	(2,886)	5,647	13,703
Uses					
Working Capital					
Increases (Decreases) to inventory	180	63	115	190	475
Increases (Decreases) to receivable	140	98	321	1,100	2,300
(Increases) Decreases to payables	(92)	(77)	(335)	(569)	(908)
Total Change to Working Capital	228	84	101	721	1,867
Net Change from operations	81	(1,766)	(2,987)	4,926	11,836
Capital Purchases	78	352	550	670	825
Capital Financing	0	2,000	2,000	0	0
Total Change in cash & equivalents	3	(118)	(1,537)	4,256	11,011
Change in Cash Balance					
Beginning Cash Balance	138	141	23	(1,514)	2,742
Ending Cash Balance	141	23	(1,514)	2,742	13,753

Table 4

Balance Sheets: 2000 - 2004 (in thousands)	12/31/00	12/31/01	12/31/02	12/31/03	12/31/04
Assets					
Current Assets					
Cash	141	23	(1,514)	2,742	13,753
Accounts Receivable	140	238	559	1,659	3,959
Inventory	280	343	458	648	1,123
Total Current Assets	561	604	(497)	5,049	18,835
Plant & Equipment					
Capital/Office Equipment	165	517	1,067	1,737	2,562
Less: Depreciation	6	37	93	252	489
Total Equipment Assets	159	480	974	1,485	2,073
Total Assets	**720**	**1,084**	**477**	**6,534**	**20,908**
Liabilities & Owners' Equity					
Current Liabilities					
Accounts Payable	92	169	504	1,073	1,981
Other Payables	0	0	0	0	0
Total Liabilities	92	169	504	1,073	1,981
Owner/Stockholder Equity					
Common Stock	781	2,781	4,781	4,781	4,781
Retained Earnings (Deficit)	(153)	(1,866)	(4,808)	680	14,146
Total Owners' Equity	628	915	(27)	5,461	18,927
Total Liabilities & Equity	**720**	**1,084**	**477**	**6,534**	**20,908**

Table 5

imperium
Advanced ultrasonic imaging

August 29, 2001

NASA Center for Aerospace Information
Attn: Document Processing Section
7121 Standard Drive
Hanover, MD 21076-1320

Dear Sir or Madam:

Enclosed please find our Phase I Final Report including CD-ROM for the NASA SBIR Contract # NAS9-01028. We hope you find the report helpful and look forward to the prospects of working together on a subsequent Phase II.

If you have any questions, please give me a call at 240-453-6236.

Best regards,

Bob Lasser

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